Bioactive Materials 18 (2022) 178–198

Contents lists available at ScienceDirect

Bioactive Materials

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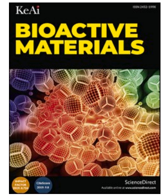

Review article

Junctional epithelium and hemidesmosomes: Tape and rivets for solving the "percutaneous device dilemma" in dental and other permanent implants

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A R T I C L E I N F O

Keywords:
Percutaneous device
Percutaneous implant
Hemidesmosome
Junctional epithelium
Bioinspired surfaces

A B S T R A C T

The percutaneous device dilemma describes etiological factors, centered around the disrupted epithelial tissue surrounding non-remodelable devices, that contribute to rampant percutaneous device infection. Natural percutaneous organs, in particular their extracellular matrix mediating the "device"/epithelium interface, serve as exquisite examples to inspire longer lasting long-term percutaneous device design. For example, the tooth's imperviousness to infection is mediated by the epithelium directly surrounding it, the junctional epithelium (JE). The hallmark feature of JE is formation of hemidesmosomes, cell/matrix adhesive structures that attach surrounding oral gingiva to the tooth's enamel through a basement membrane. Here, the authors survey the multifaceted functions of the JE, emphasizing the role of the matrix, with a particular focus on hemidesmosomes and their five main components. The authors highlight the known (and unknown) effects dental implant – as a model percutaneous device – placement has on JE regeneration and synthesize this information for application to other percutaneous devices. The authors conclude with a summary of bioengineering strategies aimed at solving the percutaneous device dilemma and invigorating greater collaboration between clinicians, bioengineers, and matrix biologists.

1. Introduction to "percutaneous device dilemma" in dental and other permanent implants

Cellular attachment to extracellular matrices is a requisite for tissue function and contributed to the rise of multicellular life [1]. Cells without a matrix would exist as amorphous masses without a physical environment. Physical and (bio)chemical factors provide a compendium of signaling effectors for cells to interrogate, react, and remodel [2]. Interplay between cell and matrix, or dynamic reciprocity [3,4], mediates tissue homeostasis and disease through pathways and mechanisms as diverse as the matrisome itself [5]. Yet, oftentimes, diseased or damaged tissue treatment requires material-based therapies and interventions.

Integration of matrix biology and bioengineering has contributed to notable progress in tissue regeneration [6]. Appreciation of 850 million years of matrix evolution [7] has led bioengineers to beg, barter, and steal from that rich repository of biomolecules to recapitulate and potentiate regenerative functions. However, implanted biomaterials meant for long-term usage such as some indwelling catheters, osseointegrated prostheses for limb amputation treatments, and dental implants are – necessarily – composed of decidedly non-matrix polymers, ceramics, and metals, for long-term service [8]. A major subset of permanently implanted biomaterials are percutaneous, or penetrate and pass through an epithelial tissue [9]. Juxtaposition of a non-matrix, permanent biomaterial – unable to actively participate in dynamic reciprocity – in a living tissue has led to the "percutaneous device dilemma."

The percutaneous device dilemma, identified by von Recum [10],

Peer review under responsibility of KeAi Communications Co., Ltd.

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https://doi.org/10.1016/j.bioactmat.2022.03.019
Received 12 November 2021; Received in revised form 14 February 2022; Accepted 12 March 2022
Available online 19 March 2022
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describes etiological factors, centered around the disrupted epithelial tissue surrounding non-remodelable devices, that contribute to rampant percutaneous device infection [11]. The dental implant/epithelium typifies this interface and is marked by "physical adaptation" of the epithelium rather than "biological attachment" like the original organ, the tooth [12]. Resultant device infection and failure leads to additional surgical interventions, contributes to antimicrobial resistance, and can lead to mortality [13–16]. For example, one million dental implants worldwide fail. Reports for indwelling catheters, which may be left in place permanently in some cases, demonstrate 80,000 infections per year [17–20]. Natural percutaneous organs, in particular their extracellular matrix mediating the "device"/epithelium interface, serve as exquisite examples to inspire design of longer lasting percutaneous devices meant for long-term use (Fig. 1).

The human tooth can survive someone's entire lifespan. This durability and imperviousness to infection is mediated by the epithelium directly surrounding it, the junctional epithelium (JE). The JE is a stratified, squamous, non-keratinized, incompletely differentiated, epithelial component composed of keratinocytes arranged parallel to the tooth surfaces; 15–30 cells thick coronally and 1–3 cells thick apically [21,22]. The hallmark feature of JE is formation of hemidesmosomes (HDs) by keratinocytes. HDs are cell/matrix adhesive structures that attach surrounding oral gingiva to the tooth's enamel through a basement membrane [23,24]. Indeed, debilitating oral phenotypes, all typified by gingival detachment from the tooth, are observed with missing or mutated JE or HD structural components [25,26]. JE-inspired strategies, based in durable tooth attachment vis-à-vis HD expression, are poised for exploitation to extend percutaneous device lifespans for long-term use.

In this review, we survey the multifaceted functions of the JE, emphasizing the role of the matrix, with a particular focus on HDs and their five main components. We highlight the known (and unknown) effects dental implants – as a model percutaneous device – placement has on JE regeneration and synthesize this information for application to other percutaneous devices. We conclude our narrative review with a summary of bioengineering strategies aimed at solving the "percutaneous device dilemma" of devices meant for long-term implantation. Finally, we provide an outlook on future strategies and potential avenues of innovation, with a focus on stimulating greater collaboration between clinicians providing percutaneous device therapies, bioengineers, and matrix biologists. Answering these questions will widen opportunities to harness extracellular matrix to create the next generation of long-lasting percutaneous devices meant for long-term use with "an absolute bacterial barrier, being tenacious in its attachment, and having the strength and durability for long-term function." [27].

2. Junctional epithelium: tape attaching the gingiva to teeth

2.1. Overview of the junctional epithelium and its unique basement membrane

The JE is a unique epithelial component at the challenging border between the oral cavity, the oral epithelium, and teeth. The JE, as an attachment complex between oral epithelium and tooth that originates from the enamel organ during tooth development [28], faces the gingival connective tissue and tooth surface (Fig. 2a) [29]. A basement membrane, the external basal lamina (EBL), is secreted between the JE basal cells and the gingival connective tissue (Fig. 2b). On the opposite side, an additional basement membrane, the internal basal lamina (IBL), forms an interfacial matrix between the tooth surface-facing JE cells (sometimes known as directly attached cells; DATs) and the tooth (Fig. 2c) [30]. Basal cells near the gingival interface at the cemento-enamel junction (CEJ) are cuboidal shaped whereas the rest of JE cells are flat and oriented parallel to the tooth surface [31]. The JE attachment to teeth has been frequently described as a "biological seal" or "tape" that functions as a barrier against microbial colonization and infection.

The hallmark JE feature is an abundance of HDs (Fig. 2d and **e**) [32,

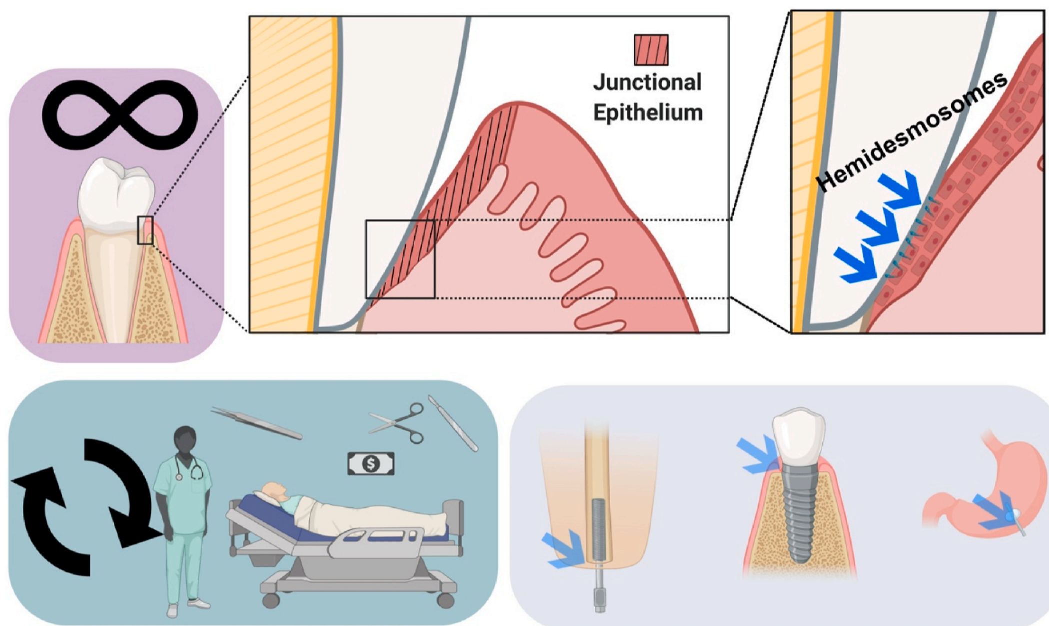

Fig. 1. Junctional epithelium, the matrix hemidesmosomes, and percutaneous device failure. The percutaneous tooth can survive someone's entire life span (infinity symbol). This marked longevity is enabled through the unique basement membrane, the junctional epithelium, that mediates durable, robust attachment through formation of cell/matrix adhesive structures, hemidesmosomes (blue arrows), by keratinocytes. Unfortunately, modern percutaneous devices like orthopaedic limb prostheses, dental implant, and gastrostomy tubes suffer from the "percutaneous device dilemma" leading to costly revision (repeat symbol) surgeries from infection. Junctional epithelium-inspired strategies, like hemidesmosome formation around such devices, are poised for exploitation to extend percutaneous devices for long-term lifespans. Image created with BioRender (biorender.com). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

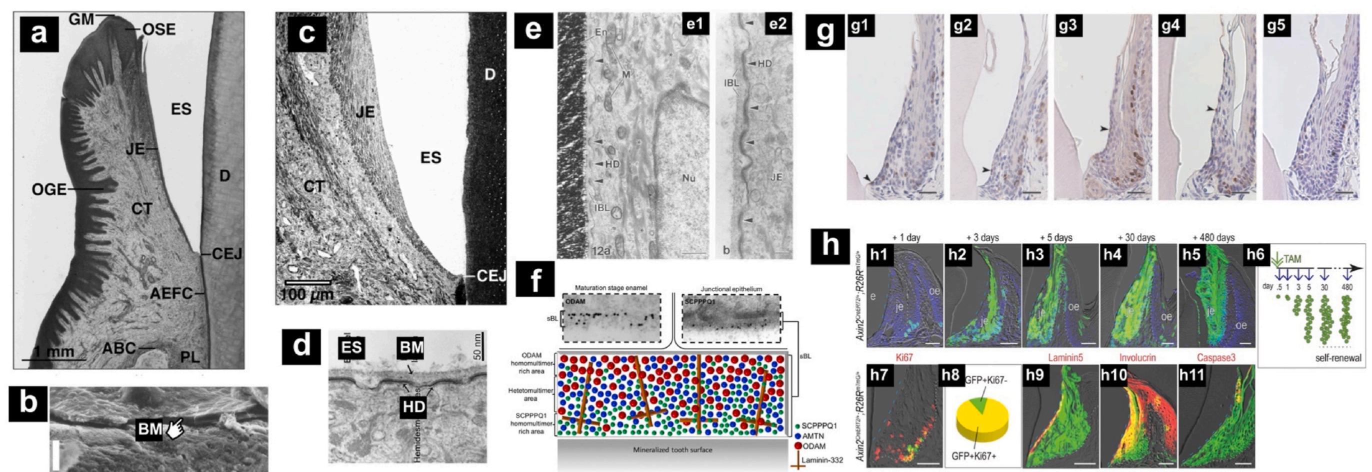

Fig. 2. Junctional epithelium structure, major components, and key functional properties. a. Light microscopy of a human gingiva and junctional epithelium from a healthy, young patient. Scale bar is 1 mm. Image used with the permission of SAGE Publications Inc [39]. **b.** On-edge view from scanning electron microscopy of JE basement membrane juxtaposed against the tooth. Scale bar is 5 μm. Image used and adapted with the permission of Wiley [33]. **c.** Back-scattered scanning electron microscopy of the apical, tapered portion of the human junctional epithelium. Scale bar is 100 μm. Image used and adapted with the permission of SAGE Publications Inc [39]. **d.** Transmission electron microscopy with prominent electron-dense plagues or rivets of hemidesmosomes formed by resident keratinocytes. Scale bar is 50 nm. Image used and adapted with the permission of Wiley [74]. **e.** Transmission electron microscopy of junctional epithelium-resident cells (keratinocytes) forming hemidesmosomes in a linear array **(e1**; scale bar is 0.5 μm**)** immediately adjacent to the tooth **(e2**; scale bar is 0.1 μm**)**. Arrows denote hemidesmosomes (HDs). Image used with the permission of Wiley [33]. **f.** Schematic of the distribution of amelotin (AMTN), odontogenic ameloblast-associated protein (ODAM), and secretory calcium-binding phosphoprotein proline-glutamine rich 1 (SCPPPQ1) in relation to laminin332. Immunogold electron microscopy images are inset. No scale bars provided. Image used with the permission of Nature Publishing Group [59]. **g.** Mouse junctional epithelium immunohistochemically prepared with 5-bromo-2-deoxyuridine (BrdU), a marker of cell division. BrdU-positive cells are seen after 2 h (**g1**), 6 h **(g2)**, 12 h **(g3)**, 24 h **(g4)**, and 48 h **(g5)** post-BRU-injection, suggesting a relatively high proliferative capacity. Scale bar is 20 μm. Image used with the permission of Wiley [36]. **h.** Wnt-responsive stem cells visualized through green fluorescent protein reporter (nuclei stained in blue) at 1 day (**h1**), 3 day (**h2**), 5 day (**h3**), 30 day (**h4**), and 480 day (**h5**) reporter chase. Schematic (**h6**) showing lineage tracing design where mice received 1 dose of tamoxifen (TAM) to label Wnt-responsive cells. Wnt-responsive cells (1 day chase) co-stained with Ki67, a proliferation marker **(h7)**, and fraction of Ki67+ green fluorescent protein + cells (double positive) of total green fluorescent protein + cells (**h8**). Wnt-responsive population (in green) of a 5 day chase was co-stained with laminin-5/laminin332 (**h9**), involucrin (**h10**), and caspase 3 (**h11**). Scale bar is 50 μm. Image used with the permission of SAGE Publishing Inc [75]. ABC, alveolar bone crest; AEFC, acellular extrinsic fiber cementum; CEJ, cemento-enamel junctional; CT, gingival connective tissue; D, dentin; ES, enamel space; GM, gingival margin; JE, junctional epithelium; OGE, oral gingival epithelium; OSE, oral sulcular epithelium; PL, periodontal ligament; BM, basement membrane; HD, hemidesmosomes; En or E, enamel; IBL, internal basal lamina; M, mitochondria; Nu, nucleus; sBL, specialized basal lamina. Scale bar is 50 μm. Image used with the permission of SAGE Publishing Inc [75]. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

33]. These cell-matrix adhesive structures are a direct result of the unique basement membrane in the JE. Basement membranes, extracellular matrices that coat and enrobe epithelial cells, are prototypically composed of laminin, type IV collagen (a "chickenwire" forming collagen), nidogen (also known as entactin), and perlecan [34]. Laminin and type IV collagen networks assemble and are linked together by nidogens and perlecans; these biomolecular meshes input physical and (bio)chemical signal into cells and are constantly remodeled [35]. However, the JE basement membrane is atypical.

The IBL, mediating JE/tooth attachment, does not contain type IV collagen, perlecan, nidogen-1, nor the (almost) ubiquitously expressed laminin111. Instead, the IBL is almost completely composed of laminin332 at a 12-fold higher concentration than any other oral epithelium [36]. This odd IBL composition has resulted in some questioning whether the IBL is a true basement membrane or not [37]. Regardless, the IBL appears to contain two major sub-layers, the lamina densa (LD) and the lamina lucida (LL), under electron microscope evaluation but their functional significance is unclear and may result from microscopy preparation (dehydration for example) [24]. Remarkable laminin332 expression facilitates laminin332-dependent HD formation to link JE cells to the IBL matrix on the tooth. In contrast, the EBL, mediating JE/gingiva attachment, contains type IV collagen, perlecan, nidogen-1, and, at least, laminin332, laminin111, and laminin511 like many typical basement membranes (Fig. 2f). A detailed summary of the biomolecular contents of IBL, EBL, and JE in cases where distinctions between IBL and EBL are not made, is found in Table 1.

The JE, as noted, is stratified, squamous, non-keratinized, and incompletely differentiated [21,22]. Exfoliation of daughter cells occurs at the free surface of the JE as cells migrate toward the coronal surface and desquamate. This occurs rapidly; JE turnover takes 1–6 days compared to 12 days for surronding mucosal tissue or a month for typical skin (Fig. 2g) [22]. Both basal and suprabasal cells have the ability to divide and turnover during minor injury, suggesting that repair and regeneration takes place from within the JE itself (Fig. 2h) [38]. JE residents cells are connected with few desmosomes and gap functions compared to surrounding tissue, leading to wide intercellular spaces between cells [31]. This space enables gingival crevicular fluid flow, a solution similar to saliva and rich in biomolecules, and immunological cell migration (chiefly mononuclear leukocytes) [39]. JE resident cells have numerous microvillous cytoplasmic processes and abundant intracytoplasmic vacuoles, all likely related to frequent phagocytosis of microbial challenges, compared to the rest of the oral epithelium [21]. A complete detailing of differences between JE and oral epithelium may be found elsewhere [22]. Characteristics of the junctional epithelium are shown in Fig. 2.

2.2. Overview of hemidesmosomes, key cell/matrix adhesive structures in the junctional epithelium as "rivets"

HDs stably anchor epithelial cells to basement membranes, like keratinocytes in the JE, by linking the cytoskeletal keratin intermediate filament network and the aforementioned obligate extracellular laminin332 [76]. Classical Type I HDs (Fig. 3a), which are found in stratified and pseudostratified epithelia, are composed of (**1**) transmembrane

Table 1
Summary of notable biomolecules in the oral junctional epithelium. Investigations proving certain biomolecules of interest were not expressed are included. "Ambiguous" refers to those papers not explicitly subdividing the JE into IBL and EBL; indeed, most modern investigations do not subdivide the JE. Abbreviations: X, expressed; Var, variable; Neg, negative; IBL, inner basal lamina; EBL, external basal lamina; JE, junctional epithelium.

Biomolecule	Localization			Reference
	IBL	EBL	JE (ambiguous)	
Laminins				
Laminin332	X	X		[22,23,36,40–44]
Laminin511		X		
Laminin111		X		
Laminin subunit α1		X		
Laminin subunit α2			Neg	
Laminin subunit α4			Neg	
Laminin subunit α5		X		
Laminin subunit β1		X		
Laminin subunit β2			Neg	
Laminin subunit γ1		X		
Laminin subunit γ3			Neg	
Integrins				
Integrin α2β1			X	[40,42,45]
Integrin α3β1	X	X		
Integrin α5β1			Var	
Integrin α6β4	X	X		
Integrin αvß6			X	
Integrin subunit α4			Neg	
Integrin subunit α2			X	
Integrin subunit α3			X	
Integrin subunit α6			X	
Integrin subunit β1			X	
Integrin subunit β4			X	
Keratins				
Keratin 1			Neg	[22,46,47]
Keratin 2			Neg	
Keratin 4			Neg	
Keratin 8			X	
Keratin 9			Neg	
Keratin 10			Neg	
Keratin 11			Neg	
Keratin 13			X	
Keratin 16			X	
Keratin 17			X	
Keratin 18			X	
Keratin 19			X	
Syndecans				
Syndecan 1			X	[48]
Syndecan 2			Neg	[48]
Syndecan 3			X	[48]
Syndecan 4			X	[48]
P-cadherin			X	[49]
Others				
Collagen IV		X		[44,45]
Collagen VII		X		[50]
Perlecan		X		[50]
Nidogen-1		X		[42]
Tenascin C	X	X		[42]
Fibronectin			Var	[43,51]
Versican	X	Var		[52]
Heparin sulphate proteoglycans		X		[53]
Secretory leukocyte protease inhibitor			X	[54]
Human neutrophil defensins 1-3			X	[55]
Human β-defensins 1 and 2			Neg	[55]
LL-37			X	[54,55]
S100A8 and S100A9 (calprotectin)			X	[56]
Follicular dendritic cell-secreted protein			X	[57]
Odontogenic ameloblast-associated protein	X			[58]
Amelotin	X			[59]
Secretory calcium-binding phosphoprotein, rich in proline and glutamine 1			X	[60]
E-cadherin			X	[61,62]
Claudin-1			X	[62]
Carcinoembryonic antigen-related cell adhesion molecule 1			X	[63]
Interleukin-8			X	[64]
Intercellular adhesion molecule-1			X	[65]
Epidermal growth factor			X	[66]
Keratinocyte-derived chemokine			X	[67]
Macrophage inflammatory protein-2			X	[67]
Interleukin-1β			X	[67]
Tumor necrosis factor			X	[67]
N-acetyllactosamine			X	[68]
Transferrins			X	[69]
Substance P			X	[70]
Calcitonin gene-related peptide			X	[71]
Nerve growth factor receptor			X	[70]
Connexin 26			X	[72]
Transient receptor potential cation channel subfamily vanilloid member 4			X	[73]

receptor integrin α6β4, (**2**) plectin, (**3**) CD151, (**4**) BP230 (which is also called bullous pemphigoid antigen 1 isoform e; BPAG1e) and (**5**) collagen XVII (which is also called BP180 or BPAG2). HDs are well known for their role in dermal/epidermal cohesion, where alterations in HD structure lead to skin fragility, blistering, and potential mortality [77,78]. Debilitating oral phenotypes are simultaneously seen in the JE due to such mutations [25,26]. On the other hand, Type II HDs, found only in simple epithelia such as the intestine, consist of only (**1**) integrin α6β4 and (**2**) plectin [79]. Our focus is Type I HDs, which will be simply referred to as "HD" henceforth, as Type I are those HDs found in the JE. An overview of hemidesmosomes and their components is demonstrated in Fig. 3, where electron microscopy reveals HDs to be shaped, and function as, "rivets" or "studs."

2.2.1. The role of integrin α6β4 in hemidesmosomes as the "trigger"

Integrin α6β4 is one of two HD transmembrane components, the other being collagen XVII (detailed later in Section 2.2.5). Integrin α6β4 is a non-covalently linked, heterodimer of integrin subunits α6 and β4 that binds laminin332, thus "triggering" HD formation [82]. Integrins subunits α6 and β4 are comprised of extracellular, intracellular, and transmembrane domains like typical integrins [83]. (A detailed review of integrins may be found in Bachmann et al. [84]).

Integrin subunit α6 (Fig. 3b) is a prototypical α subunit composed of a folded, seven-bladed β-propeller head domain, a thigh domain, and two calf domains [85,86]. Unlike many α subunits, integrin subunit α6 does not contain an additional domain within the β-propeller domain to bind divalent metal cations [a metal-ion-dependent adhesive site (MIDAS) for cations like Mg^{2+}] [87]. Two major α6 regions afford conformational flexibility: **1**) the linker between the β-propeller and the thigh and **2**) the knee at the bend between the thigh and the calf-1 domain [88,89]. Concomitant with its function, this knee is close to a flexibility point in the β integrin subunit to allow coordinated conformational changes [84].

The transmembrane (TM) region for integrin subunit α6 is a typical (approximately) 25 amino acid region that forms a α-helical coiled structure [90]. The association between integrin subunits α and β at the TM region results in an inactive, "resting" receptor whereas separation is required for activation/ligand binding [91]. These α and β associations are generally dependent on salt-bridges, although other models have

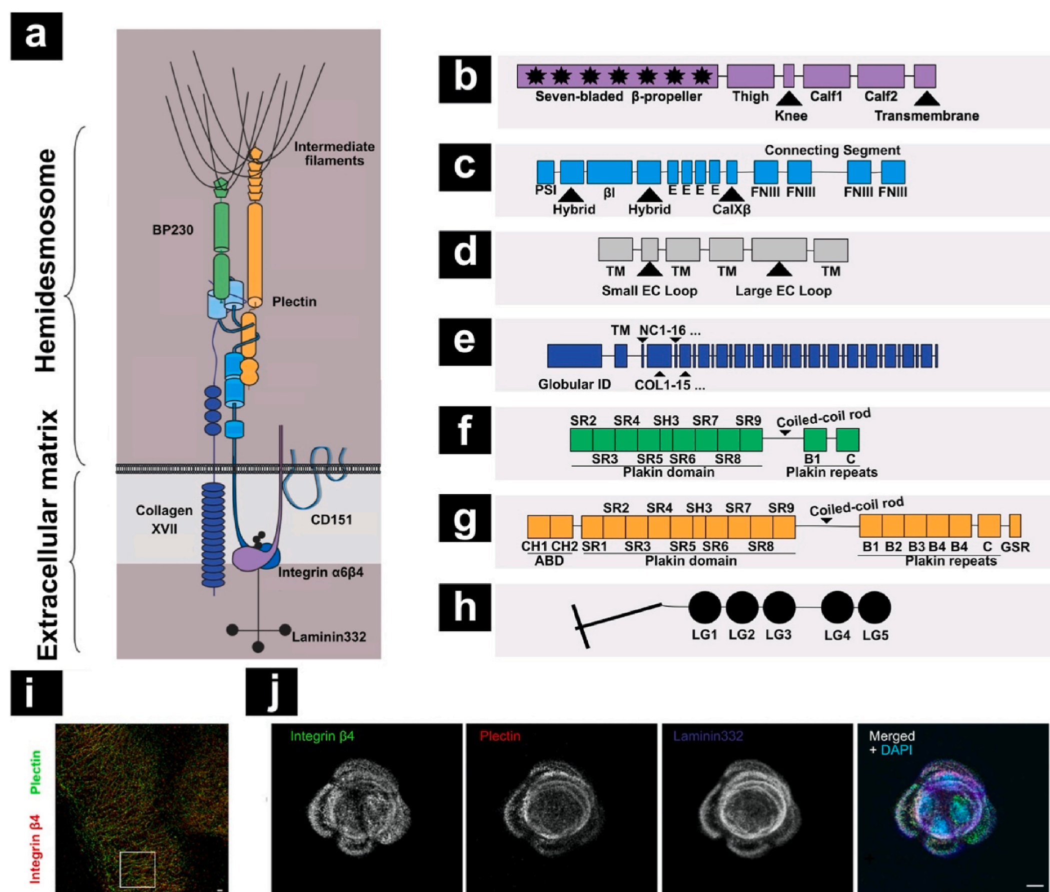

Fig. 3. Hemidesmosome structure and main components. a. Schematic drawing of the hemidesmosome showing BP230, plectin, collagen XVII, CD151, and heterodimerized α6β4 and partners laminin332 and intermediate filaments. Image used and adapted with the permission of Elsevier [76]. **b.** Structure of integrin subunit α6; a "trigger." Key domains are noted but are not necessarily to scale. **c.** Structure of integrin subunit β4; a "trigger." Key domains are noted; PSI, plexin-semaphorin-integrin; E, epidermal growth factor; CalXβ, membrane-proximal Na^{+} - Ca^{2+} exchanger; FNIII, type III fibronectin. **d.** Structure of CD151; a "nucleator." Key domains are noted; EC, extracellular; TM, transmembrane. **e.** Structure of collagen XVII; a "binder." Key domains are noted; ID, intracellular domain; TM, transmembrane; NC, noncollagenous; COL, collagen. **f.** Structure of BP230; a "stabilizer." Key domains are noted; SR, spectrin repeat; SH3, Src homology-3; B1 and C refer to names of plakin domains. **g.** Structure of plectin; a "recruiter." Key domains are noted; CH, calponin homology; GSR, glycine-serine-arginine; ABD, actin-binding domain; SR, spectrin repeat; SH3, Src homology-3; B1-5 and C refer to names of plakin domains. **h.** Selected structure of laminin332 globular domains. Key domains are noted; LG, globular domain. LG4 and LG5 are enzymatically cleaved to activate laminin332 and reveal integrin binding domains within LG1-3. **i.** Superresolution microscopy (total internal reflection fluorescence) of integrin subunit β4 and plectin in mouse-derived keratinocytes; close juxtaposition/co-localization of biomolecules is noted. Scale bar is 500 nm. Image used and adapted with the permission of The American Society for Cell Biology [80]. **j.** Confocal microscopy of integrin subunit β4, plectin, and laminin332 in immortalized junctional epidermolysis bullosa associated with pyloric atresia keratinocytes; again, close juxtaposition/co-localization of biomolecules is noted. Scale bar is 20 μm. Image used and adapted with the permission of Rockefeller University Press [81].

been introduced on how α and β TM domains interact [92,93]. However, like many other α6 or β4 integrin subunit domains, no sufficient X-ray crystal structures are available of the integrin subunit α6 TM region [94]. Likewise, the cytoplasmic region is also unresolved, which is complicated by integrin subunit α cytoplasmic domains high divergence [95]. This unknown structure is related to flexible and transient structures when not stabilized by other proteins [96]; little is known about proteins that interact with the integrin subunit α6 intracellular domain [92]. Mutations in integrin subunit α6 may lead to oral pemphigoid epidermolysis or junctional epidermolysis bullosa with pyloric atresia (JEB-PA) in humans [97].

Integrin subunit α6 may heterodimerize with integrin subunit β1 to form α6β1, which like α6β4, binds laminins like laminin α5 chain–containing laminin511 and laminin521 isoforms [98]. This "choice" for the heterodimerizing partner of subunit α6 (α6β1 vs. α6β4) is partially controlled by the α6 integrin subunit messenger RNA (mRNA) untranslated region (UTR) regulating the site of translation via a "zipcode" sequence [99]. Integrin subunit α6-laminin interactions are prototypically associated with arterial walls [100], kidney integrity [101], and, embryonic development [102] wherein subunit α6 is a marker for at least 30 stem cells populations including hematopoietic progenitors [103]. The expression of α6A and α6B isoforms, generated by alternative mRNA splicing [104], is regulated by ESRP1-splicing factor (epithelial splicing regulatory protein 1) and results in a more highly charged α6B compared to α6A due to a frameshift deletion [105, 106]. The functional differences between integrin subunit isoforms α6 are unresolved although it is known the isoform ratio can predict stem cell differentiation state; α6A expression is upregulated over α6B in differentiating or differentiated stem cell populations compared to undifferentiated [107,108].

Integrin subunit β4 (Fig. 3c) is an unusual integrin subunit due to its long cytoplasmic tail pivotal to HD formation; absence or mutation of integrin β4 leads HD loss in both humans [JEB-PA or junctional epidermolysis bullosa-Herlitz (JEB-H)] and genetically modified animals [109,110]. Indeed, integrin subunit β4 can associate with almost all hemidesmosomal proteins and effectors [111]. The 1000+ residue β4 tail links integrins to the HD cytoskeletal structure [112,113] composed of intermediate filaments keratin 5 and keratin 14 in HDs [114]. This

keratin linkage is rather unique amongst integrins as most integrins are associated with the actin filament network [115].

The TM domain of integrin subunit β4 is typical of integrins; rich in GXXXG domains that facilitate "tilting" when activated [93,116]. The integrin subunit β4 ectodomain is comprised of a plexin-sempahorin-integrin (PSI) domain, a hybrid domain, and a βI domain. The βI domain is inserted in a hybrid domain, which is inserted in a plexin-PSI domain; this is known as a β-sandwich [117]. This arrangement endows a typical integrin subunit β with more flexibility than a typical integrin subunit α [93]. The βI domain contains Mg^{2+} coordinating MIDAS and an adjacent site that binds an inhibitory Ca^{2+} ion (an ADMIDAS site). The small PSI domain is divided in two halves connected by a disulfide bond [96]. These domains are followed by cysteine-rich epidermal growth factor (EGF) module [118]. Finally, the integrin subunit β4 tail is composed of five regions: **1**) a membrane-proximal Na^{+} - Ca^{2+} (CalXβ) exchanger domain, **2** and **3**) a pair of type III fibronectin (FnIII) domains, **4**) a connecting segment (CS) that separates the two FnIII domains, and **5**) a C-terminal tail [79,119]. The numerous interactions that the integrin subunit β4 tail has - critical for HD formation - will be detailed in later sections.

Integrin α6β4, despite its role in epithelial HD formation, has been reportedly expressed in non-epithelial cells such as neurons [120], astrocytes [121], Schwann cells [122], and endothelial cells that all lack HDs [123]. The role α6β4 plays in such cells is diverse, and in many cases controversial, but there is agreement that α6β4 broadly regulates migration and motility [124]. For example, integrin α6β4 and ErbB-2 (a receptor protein kinase) cooperate to promote PI3K (phosphoinositide 3-kinase)-dependent invasion in many cancers [125–128]. Integrin α6β4-mediated migration and motility is related to the general role of integrins in surveying the extracellular matrix and activating Rho GTPases (hydrolase enzymes that help produce guanosine diphosphates). For example, Rac, a commonly expressed Rho GTPase, modulates cytoskeletal reorganization and actin-rich lamellipodia extension [129]. Rac activation leads to downstream myosin light chain (MLC) kinase phosphorylation, which activates myosin II to create actin-myosin contraction forces [130,131]. Indeed, integrin α6β4 involvement in the Rho-ROCK (Rho-associated protein kinase)-MLC and FAK (focal adhesion kinase)-PI3K signaling pathways has been well demonstrated [81]. Generation of such signaling hubs at integrins likely drives the 135 integrin α6β4 interactors [132].

2.2.2. The role of plectin in hemidesmosomes as the "recruiter"

Plectin (Fig. 3g) is a cytoskeletal linker protein from the plakin family. Plakins, which are also referred to as cytolinkers, link cytoskeletal elements together and to adhesive-junctions like HDs [133]. Plectin is composed of N- and C-terminal domains separated by a central α-helical coiled-coil rod domain [134]. The N-terminal region contains two calponin homology domains (CH1 and CH2) that together form the actin-binding domain (ABD) [135]. The ABD binds to integrin α6β4 [136], nesprin-3α [137,138], F-actin [139], and dystrophin [140]. These interactions, where plectin functions as "recruiter," are essential for resisting actomyosin contractility and traction force generation [81]. The ABD is followed by a plakin domain, which consists of nine spectrin repeats and a Src homology-3 domain, and binds integrin subunit β4 [141]. Each spectrin repeat is composed of three α-helices that form an antiparallel triple helical bundle [142]. These plakin domains also bind intermediate filaments, where each domain has affinities for different intermediate filaments [143,144].

Plectin's C-terminus tail is made of six plakin repeat domains with a linker in between the fifth and sixth domains, and a glycine-serine-arginine (GSR)-rich domain. GSRs are thought to act as a microtubule binding domain [145]. The central rod domain is responsible for homodimerization via coiled-coil interactions to associate into stable polymers that aid HD stabilization [79,135]. Plectin exists as eight isoforms; HDs are associated with plectin 1a [133]. Other isoforms are highly expressed, for example plectin 1c is the most abundant isoform in the epidermis, but play no apparent role in HD formation [146]. This is likely due to the N-terminal isoform-specific sequences on plectin 1a that mediates calcium-dependent interactions with integrin subunit β4 [147].

Integrin subunit β4 interacts with plectin through plectin's ABD and a region comprised of the first fibronectin type III (FnIII) pair domains and an adjacent connecting segment (Fig. 3i and **j)**. A secondary interaction occurs between plectin's plakin domain and the ultimate C-tail of integrin subunit β4 [76,141,148,149]. The integrin α6β4–plectin interaction is a pivotal first step in HD formation and facilitates collagen XVII and BP230 recruitment [141]. Structural consequences in plectin-deficient genetically modified mice are seen by post-birth death due to epithelial detachment; neither collagen XVII nor BP230 are effectively recruited into HDs [150,151]. Humans with plectin mutations also suffer skin fragility [epidermolysis bullosa with muscular dystrophy (EB-MD)]; most mutations are in the rod domain despite that fact that rodless plectin and full-length plectin have largely redundant functions [80,152].

2.2.3. The role of BP230 in hemidesmosomes as the "stabilizer"

BP230 (Fig. 3f), also known as BPAG1e, is another plakin involved in HD formation. BPAGs exist as three isoforms which differ in plakin repeat domains and spectrin repeats [153]. BP230 specifically is structurally similar to plectin but lacks an ABD and has only two plakin repeat domains joined by a linker without spectrin repeat domains [133]. BP230 binds α6β4, collagen XVII, and keratin 5 and keratin 14 and therefore further "stabilize" HDs [154,155]. BP230's plakin domain interactions with the second FNIII repeats pair in integrin subunit β4 [150] and its N-terminal domains interacts with the collagen XVII N-terminal domains [156]. Finally, BP230's C-terminal tail interacts with intermediate filaments [157]. The BP230 rod domain can also form heterodimers with plectin *in vitro* [79].

Genetically modified mice lacking BP230 have poorly formed HDs and fragile skin with delayed wound healing; humans with mutated BP230 suffer from bullous pemphigoid [157]. BP230 has been implicated in keratinocyte migration, where BP230-deficient cells have defects in front–rear polarity, reduced lamellipodial stability, and loss of directionality [158]. The earlier noted integrin α6β4 control over Rac is partially regulated by BP230 and cofilin (an actin-severing protein) activity [159]. Non-functional BP230 has also been shown to increase integrin subunit β1 activation and keratin 14 expression [160]. Nuclear BP230 has also been observed, although its significance is unclear [161].

2.2.4. The role of CD151 in hemidesmosomes as the "nucleator"

CD151 (Fig. 3d) is a cell surface protein from the tetraspanin family. Tetraspanins are characteristically composed of four TM domains (hence the name), a small and a large extracellular loop, and short intracellular N- and C-terminal tails [162]. CD151, like all tetraspanins, functions as an organizer by assembling multimolecular complexes of cell surface receptors like integrins and cadherins. CD151 forms complexes, or "nucleates," other integrins, notably α3β1 (an extremely strong association [163]), α6β1, α6β4, and α7β1, and is expressed by epithelial and mesenchymal origin cells [164]. CD151's association with integrin α3β1 forms 'pre-hemidesmosomal' clusters at the basal keratinocyte surface that serve as "nucleation sites" for the HD assembly by α6β4 [165]. These clusters help to facilitate eventual α6β4-plectin associations [76]. Such CD151-integrin subunit α6 interactions occur at the large CD151 extracellular loop [164,165]. CD151 is the only tetraspanin protein associated with HDs, despite structural similarities to all other tetraspanins [164]. Mutations in CD151 are associated with human skin fragility, such as Kindler syndrome-like epidermolysis bullosa [166,167].

CD151 has historically been difficult to study because of its interactions with many integrins and its role in integrin trafficking. However, a recent study definitively proved core CD151 functions that had previously only been hinted at [168]. CD151, through its binding to

integrin α3β1, is necessary for HD formation and stabilization and strengthening integrin α3β1-, but not integrin α6β4-, dependent keratinocyte adhesion to laminin332. After laminin332 deposition and CD151-mediated integrin α3β1 clustering to pre-nucleated α6β4-mediated integrins, CD151 is unnecessary for further HD development. Concomitantly, HDs can be formed in the absence of α3β1 so long as CD151 interactions with integrin subunit β4 are fulfilled by other integrins.

Classic studies have implicated CD151 in epithelial wound healing. For example, CD151-deficient mice have impaired wound healing and reduced deposition of laminin332 [169]. Basement membrane disorganization has been ascribed to alterations in integrin α3β1 and CD151 interactions [170]. CD151 also regulates integrin trafficking during migration, wherein integrins are endocytosed from the rear of the cell and recycled to the front. The CD151 cytoplasmic tail is important in this process; endocytosis and cell migration are altered when mutated [171,172]. The CD151 cytoplasmic tail also negatively regulates Rac [163]. This tail is also recognized by adaptor protein-2 complex, a component of clathrin endocytosis [173,174].

2.2.5. *The role of collagen XVII in hemidesmosomes as the “binder”*

Collagen XVII (Fig. 3e), also known as BPAG2 (Bullous Pemphigoid Antigen 2) and BP180 (Bullous Pemphigoid, 180 kD), is a homotrimeric transmembrane protein composed of three collagen type XVII, alpha 1 chains [175]. Each collagen domain is composed of a globular-shaped intracellular domain (ID), a short TM domain, and an extracellular C-terminal domain with 15 collagen repeats (COL1–COL15) separated by 16 noncollagenous (NC1–NC16) subdomains [79]. The most membrane proximal domain NC domain serves to nucleate formation of a flexible collagen-like triple helix [176,177]. The coiled-coil extracellular domain is shed by proteases by producing a fragment (an ectodomain known as LAD-1) that is incorporated in the matrix [178–180].

Cleavage and shedding of the collagen XVII ectodomain is involved in keratinocyte detachment, migration, proliferation and wound healing [181]. LAD-1 is reportedly involved in regulated intramembrane proteolysis (RIP) [182]. Proteolytic processing is relatively common and catalyzed by the proteinases ADAM3 (a disintegrin and metalloprotease 3; the most studied proteinase in this context) and also by ADAM9, 10, and 17, as well as neutrophil elastase [183]. Cleavage sites are located about ten amino acid residues C-terminally from the coiled-coils in the NC16 domain [184].

Collagen XVII contains multiple binding sites for HD proteins, including plectin, BP230, integrin subunit β4, integrin subunit α6, and laminin332 [185,186]. As a result of all these interactions and being a prolific “binder,” collagen XVII is located in the core of the HD protein assembly [150]. Collagen XVII expression is required for proper BP230 and plectin localization [150]. It should be noted that although direct collagen XVII to laminin332 binding has been shown *in vitro*, it has insufficiently high affinity to adhere cells to laminin332 in the absence of integrin α6β4 [187]. Collagen XVII is directly involved in mitogen-activated protein kinase (MAPK) signaling pathways during cell migration and HD disassembly [188]. For example, collagen XVII-deficient keratinocytes show high migratory behavior and decreased cell-matrix adhesion [179]. Collagen XVII can associate with actinin-4 (a spectrin protein) to regulate traction forces and actin dynamics under motile conditions [157]. Finally, animals with disrupted collagen XVII function have disrupted epithelia due to abnormalities in HD ultrastructure and usually die within several weeks after birth [189]. Human collagen XVII mutations lead to epidermolysis bullosa acquisita, among other diseases [97].

2.2.6. *Laminin332 in the matrix and hemidesmosomes*

Laminin332 (Fig. 3h) consists of three disulfide-linked glycoprotein chains (α3, β3, and γ2) that assemble in the endoplasmic reticulum into a T-shaped (the prototypical laminin cross-shape is associated with other isoforms like laminin111) heterotrimer [190]. Laminin332 was formerly known as laminin-5 (older terminology remains pervasive despite clear recommendations for the retirement of the term) [191] and consists of long arm of the assembled structure is an α-helical coiled-coil formed from each chain, whereas the three short arms are composed of only one chain [192]. Each arm contains laminin N- terminal (LN) domains followed by repeated rod-like laminin-type epidermal growth factor-like (LE) domains [193]. The α chain has an additional five laminin globular (LG) domains at its terminus that contain the majority of cell adhesion sites for integrins, syndecans, and dystroglycans [34]. Laminin332 is the major component of anchoring filaments that bridge epidermal basal keratinocytes and underlying dermis [194]. Absence of any α, β, or γ subunit abolishes complete laminin assembly. Dramatic consequences are realized from loss-of-function mutations in laminin332, such as abolished dermal-epidermal skin adhesion and skin fragility associated with JEB-H or cicatricial pemphigoid patients [195,196]. As a result, laminin332 delivery and genetic manipulation has been intensively researched for JEB-H therapies [197].

Laminin322, like all laminins, contains abundant cell adhesion peptides [192,198] and growth-factor sequestering domains [199]. Laminins are indeed glycoproteins. Laminin111, for example, is approximately 13–15% carbohydrate by weight; these carbohydrates are important for both assembly and cell binding but are poorly studied in laminin332 [200,201]. Deposited laminin332 demonstrates a mesh-like network structure [202]. However, laminin332 does not assemble like prototypical laminin111 and likely does not follow a “three-arm interaction” polymerization model [203–205]; the relatively truncated α3 and γ2 causes approximately half of total laminin332 in skin to exist in disulfide-linked complexes with laminin311 or laminin321 [206]. However, laminin332 polymerization is unresolved given insufficient laminin polymerization study methods.

Laminin332 is deposited under cells during wound healing and requires processing to dictate its biological effects [207]. Non-migratory keratinocytes cleave laminin332 α3 chains between LG3 and LG4 (thus releasing LG45) to form stable HD mediated by integrin α6β4 [208–210]. Laminin332 processing is thus required for HD formation [211] and preventing laminin332 processing prevents complete HD formation [212]. Upon migration, such as during wounding, unprocessed (non-cleaved) laminin332 is secreted at the leading migratory edge, which stimulates migration through integrin α3β1 [213,214]. LG1–3, associated with integrin binding, adopt a “cloverleaf” configuration to support integrin binding aided by LG45 cleavage [215–218]. Laminin332 also regulates keratinocyte polarization [219].

Both matrix metalloproteinases MMP-9 and MMP-14 are critical for laminin332 activation [220]. For example, MMP-9-deficient mice show delayed re-epithelization in a wound model due to reduced keratinocyte migration [221]. Integrin subunit β4 can also affect laminin-332 organization [222], which can in turn affects HD formation [223]. The released LG45 domain can undergo further processing and exert effects, like broad antimicrobial activity [224], chemotaxis [225], or induce further MMP activity [226,227].

Several studies have shown that HD formation can be driven entirely through interactions between the integrin subunit β4 cytoplasmic domain and plectin [228,229]. This does not mean that laminin332 does not play a role in nucleating HDs; integrin laminin332 ligation profoundly affects HD organization and density [228,229]. Rather, these studies emphasize other factors that drive plectin-integrin subunit β4 interactions, such as integrin crosstalk with integrin α3β1 akin to that mediated by laminin332, can drive HD formation on their own [76]. Despite the intense focus on integrin-LG interactions, as noted, others receptors do play a role in interacting with laminin332. For example, syndecans have affinity for LG4 [230] and increased laminin332 expression is associated with increased E-cadherin expression [231].

2.2.7. *Hemidesmosomes and focal adhesion: a sticky situation*

Focal adhesions, like HDs, are integrin-containing, multiprotein structures that link matrix to intracellular cytoskeleton (namely actin) to

transmit force and sense environments [232]. Many excellent reviews have previously been published on FAs [233–235]. It was initially thought FAs were only pro-migratory whereas HDs only anti-migratory as more stable cell-matrix interactions [217,236]. This simple view has been challenged, most prominently by imaging revealing dynamic HDs in migrating cells and not complete HD disassembly as one would conventionally expect [237]. Instead, paxillin-positive (a multi-domain adaptor protein in FAs) and actin fibers in FAs are intermingled between HDs, with actin absent from integrin subunit β4 patches [238]. One can obtain a sense for the condition-dependent localization of HDs from Fig. 3i and **j.** Coordinated “treadmilling” occurs with HD assembly at the leading cell edge and disassembly at the rear. As a result, integrin α6β4 has been described as the “master regulator” of transcription and translation for other integrin subunits related to FAs such as α2, α3, and β1 [159]. FAs are required for HD formation and HDs are needed for FA localization. For example, HDs regulate FA density [239,240], reduce traction force generated by FAs [241], and the HD-keratin complex regulates collective cell migration in addition to the oft-studied actin network [242]. HDs, like FAs, can be controlled by nanoscale geometry but this topic is vastly understudied compared to FAs [243].

2.2.8. Regulation of hemidesmosomes dis- and re-assembly by growth factors

Wound healing is typified by a complex release of growth factors [244]. This response necessary for coordinating cell migration requires keratinocyte HD dis- and re-assembly [245]. Past studies have shown activating epidermal growth factor receptor (EGFR) and protein kinase C (PKC) pathways results in destabilization of HDs through integrin subunit β4 cytoplasmic tail phosphorylation to destabilize interactions with plectin [246–248]. Detailed information about specific integrin subunit β4 cytoplasmic tail phosphorylation sites may be found elsewhere [249]. Integrin subunit β4 cytoplasmic tail phosphorylation has also been documented in response to hepatocyte growth factor (HGF) [245] and EGF [246]. Similarly, exposure of *recepteur d'origine Nantais* (RON; a receptor tyrosine kinase) to its ligand, MSP, results in RON binding plectin and disrupting plectin-integrin subunit β4 interaction, ultimately disassembling HDs [250,251]. HDs can also be stabilized by overexpression of cell adhesion molecule Necl-2 (nectin-like molecule 2) that binds integrin subunit β4 on its extracellular region [252].

2.2.9. Differences between hemidesmosome formation in vitro and in vivo

Few investigators study HD formation *in vivo.* However, a major difference has emerged between *in vitro* and *in vivo* HD renewal. Plectin, necessary for HD formation *in vitro,* is not completely necessary for *in vivo* HD formation; HDs can be formed in plectin-deficient mice [151]. This may be explained by differences in the role of collagen XVII *in vitro* compared to *in vivo*. Collagen XVII clustering on the basal side of cells *in vitro* is dependent on integrin α6β4 and plectin, as previously discussed and demonstrated in integrin subunit β4-deficient keratinocytes [253]. However, collagen XVII clustering is less dependent on integrin α6β4 and plectin *in vivo* and interacts with BP230 in the absence of plectin [254]. Regulatory requirements for HD renewal *in vivo* are unclear but are generally mediated *in vitro* by interactions between integrin subunit β4 and plectin [114,255,256].

A plausible explanation for differences between *in vivo* and *in vitro* HD investigations is the 2- vs. 3-dimensional experimental conditions. No investigations to our knowledge have been performed on HD dynamics in a 3D culture system. As has been appreciated for decades [257], cell behavior is markedly different in 2D vs. 3D [258]. Many *in vitro* culture systems have been developed by bioengineers that might be suitable for application to HDs [259]. However, these possibilities have yet to be realized. Others have suggested *C. elegans* or zebrafish as suitable animal models to study HDs given the genetic and imaging toolkits available [114].

3. Important biomolecules in junctional epithelium homeostatis and regeneration

Despite studies on JE HDs, and the large body of basic HD biology, the JE contains biomolecules other than those critical to HDs. However, no unbiased characterizations analyzing the entire matrisome, such as mass spectrometry, of JE constituents have been performed. This limitation has led to many standalone studies focusing on a lone biomolecule of interest and limited synthesis and summary of structure-function relationships in the JE. Such analyses would help continuity of research in the field. Here, we briefly highlight the known and potential roles many of these biomolecules play in the JE. A summary of known JE biomolecular contents – predominately defensive factors and matrix components – is provided in Table 1.

3.1. Defensive factors in the junctional epithelium

JE produces countless “defensive factors” that mediate the potentially-destructive bacterial and immunological milieu at the JE. **SLPI** (secretory leukocyte protease inhibitor) is a protease inhibitor produced by mucosal surfaces and epithelia lining fluids such as pulmonary connective tissues and goblet cells to protect the host from inflammatory protease activity [260]. SLPI notably targets polymorphonuclear leukocyte elastase, cathepsin G, and chymotrypsin-like enzymes [261]. *Slpi* was noted in a micro-array study as the most differentially upregulated (107.6-fold) transcript in the JE compared to surrounding oral epithelium [54]. SLPI is reportedly antimicrobial against *Staphlyococci* [262], a gram-positive bacteria genus strongly implicated in orthopaedic percutaneous surgical site infections [263]. Protease inhibitors like SLPI are important to preserve hallmark JE biomolecules that are highly sensitive to protease and bacterial degradation [264].

Human α-defensins (HADs) are small (under 30 amino acids) cationic antimicrobial peptides primarily produced by neutrophils [265]. Human neutrophil defensins (HNP) 1–3, exemplar HADs, are chemotactic to T-cells [266] and readily detectable in the JE [55]. **Human β-defensins (HBDs**; differ in disulfide bond placement compared to HADs [267]) are expressed in all human epithelial tissues [268]. However, HBD1 and HBD2 are not expressed in the JE despite the JE being under constant microbial exposure [55]. This likely relates to the JE's relative undifferentiated state; past research has shown HBD expression in differentiated stratified epithelia and epidermis [269]. **LL-37**, a 37 amino acid antimicrobial generated via degradation of a larger human cationic antimicrobial protein (hCAP18) [270], is also expressed in the JE [54,55].

S100A8 and S100A9 complex to form calprotectin, a calcium-binding protein that plays a broad role in cell growth, differentiation, survival, and cancer progress while also demonstrating antimicrobial potency against orally-relevant species [271,272]. Both S100A8 and S100A9 are expressed and colocalize in the JE in animals both with an oral microflora and germ-free animals [56]. This expression may be related, although not completely explained, by the role of calprotectin in epithelial cell resistance to bacterial invasion [273]. **Follicular dendritic cell-secreted protein (FDC-SP)**, a protein whose function is not well-understood is also expressed in the JE [57] in response to lipopolysaccharide (LPS) stimulation [274], suggesting a role mediating innate immunity activation.

3.2. Calcium-binding phosphoproteins in the junctional epithelium

Two relatively well studied proteins in the JE are **odontogenic ameloblast-associated protein (ODAM)** and **amelotin (AMTN)**. ODAM is expressed throughout the JE whereas AMTN is expressed only in the IBL directly abutting the tooth [59]. Both proteins are secretory calcium-binding phosphoproteins (SCPP) [275]. SCPPs generally stabilize calcium and phosphate ions and regulate enamel formation [74,

276–279]. JE regeneration is notable slower in *Odam* knockout mice than wildtype; observed JE is fragile (described as "flaking") and AMTN expression is concomitantly downregulated [25]. ODAM is re-expressed early in JE regeneration following gingivectomy [74] and may also promote mineralization of collagen matrices [58]. ODAM induces RhoA activity and downstream factor by interacting with Rho guanine nucleotide exchange factor 5 (ARHGEF5), a regulator of small G-proteins [280]. RUNX2 (runt-related transcription factor 2) may also be involved [281]. AMTN is also expressed during JE regeneration but only once the JE is about to establish contact with the tooth again [74,282]. Finally, AMTN and ODAM may form homo- or heteromultimers - perhaps supported by laminin332 [59] - but this has not been observed *in vivo.* [283] A structurally similar SCPP, **secretory calcium-binding phosphoprotein, rich in proline and glutamine** (**SCPPPQ1**), may also play some role in JE regeneration [60].

3.3. Adhesive receptors in the junctional epithelium

Syndecans, transmembrane proteoglycans that act as receptors of matrix glycoproteins and growth factors, share similar pathways as integrins [284,285]. **Syndecan 1** is strongly expressed in the JE and most of the gingival epithelium. However, in the JE, **syndecan 2** is not expressed and **syndecan 3** and **4** are very weakly expressed [48]. What is interesting is that syndecan 1 can interact with laminin332, which may suggest syndecan 1 plays a role in interrogation of laminin332 in the JE [230]. Syndecan 1 has also been shown to regulate cellular responses to patterned surfaces and mechanotransduction [286].

Cadherins are a family of calcium-dependent transmembrane proteins capable of sensing forces to activate mechanotransducive signaling cascades and are typically associated with cell-cell linkages [287,288]. **E-cadherin** is expressed in the JE, but is heterogeneous, weaker than surrounding tissue, and abolished during periodontal diseases [61,62]. Interestingly, laminin332 has also been shown to increase expression of E-cadherin [231]. A different report showed no JE immunoreactivity for E-cadherin but rather **P-cadherin** reactivity [49].

Connexin 26, a transmembrane protein that forms gap junctions to allow passage of ions and small molecules between cells [72], is also expressed in the JE although levels decrease under inflammatory conditions more than other gingival epithelia [61]. **Claudin-1**, an integral membrane protein for tight junction formation [289], is also expressed in the JE despite the fact that tight junctions in the JE are poorly developed compared to surrounding epithelium [62]. Another adhesion-related molecule expressed by the JE is **carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM1)** [63]. CEACAM1 guides polymorphonuclear leukocytes (PMNs) through the junctional epithelium and may regulate JE structural integrity [290]. Similarly, expression of cytokine **interleukin-8 (IL-8)** in the JE [64] chemotactically guides PMNs through the JE to other gingival tissues [291,292]. **Intercellular adhesion molecule-1 (ICAM-1)** expression increases from basal cells toward the surface of the JE and controls neutrophil migration [64,293]. Such gradients control oral commensal bacteria degradation at the JE [65].

3.4. Wound healing-related biomolecules in the junctional epithelium

EGF, a hallmark growth factor of dermal wound healing through stimulation, proliferation, and migration of fibroblasts, keratinocytes, and endothelial cells, is more highly expressed in the JE than surrounding oral epithelium [66]. This may relate to integrin subunit β4 and its participation in EGF-stimulated chemotaxis [246] or maintenance of epithelial integrity [294]. The potential role for EGF in percutaneous device/epithelial integrity is supported by a recent report showing EGF and both up- and down-stream genes were highly upregulated in soft tissue immediately surrounding percutaneous implants placed in the backs of rats [295]. EGF thus may mediate wound healing response to percutaneous device placement, perhaps by controlling HD disassembly as discussed.

Keratinocyte-derived chemokine (KC), **macrophage inflammatory protein-2 (MIP-2)**, **interleukin-1β (IL-1β)**, and **tumor necrosis factor (TNF-α)** are all more highly expressed in JE than surrronding tissue [67]. Each of these may play a role in mediating JE regeneration after damage or percutaeneous device implantation. KC and MIP-2 are a major chemoattractant for neutrophils [296,297]. On the other hand, IL-1β is an inflammatory cytokine expressed by a variety of cells [298], as is TNF-α, although TNF-α is typically associated with macrophages production [299]. The acylaminosugar **N-acetyllactosamine** is also expressed in the JE and may relate to antigen reconization [68]. Finally, **transferrins**, glycoproteins involved in iron metabolism, are found in the JE [69].

3.5. Junctional epithelium innervation

The JE is more densely innervated (trigeminal nerve fibers) than any other oral epithelium [300]. Nerve fibers run close to the coronal portion of JE and acts as sensors (mechanoreceptive, thermoreceptive, chemoreceptive, and nociceptive) and participate in neurogenic inflammation. As a result, **substance P** [70], **calcitonin gene-related peptide (CGRP),** [71] and **nerve growth factor receptor (NGFR)** [70] are all expressed in the JE. Substance P is a neuropeptide that acts both as a neurotransmitter and neuromodulator but has also been implicated in epithelial wound healing [301]. CGRP, another neuropeptide, localizes to sensory fibers and is a context dependent inflammation mediator [302]. NGFR is a receptor for NGF, an important growth factor of neuron proliferation and acts to mature T cell populations [303]. JE innervation is more slowly regenerated than surrounding soft tissue upon JE injury [304].

4. Junctional epithelium development

The exact developmental mechanisms that lead to the formation of the JE remain elusive. It is generally thought the primary JE is formed by fusion of the reduced enamel organ (REO), which is then replaced by a secondary JE (the JE present post-development) derived from the oral epithelium upon eruption of the tooth and degeneration of the REO [305]. Developmental factors that orchestrate the formation of the secondary JE are poorly studied [306]. Turnover and renewal of the JE, and whether the JE is maintained throughout life without replacement by other oral epithelium-derived cells or if a stem cell population resides within the JE (or both), remain controversial [307]. To clarify whether the JE is self-sustaining or replaced by the oral epithelium (or a combination of both), JE regeneration following gingivectomy (removal of the JE) has been studied and observed to occur for nearly 50 years [308,309] leading others to conclude regenerated JE is derived from surrounding oral epithelium [28,39,310]. However, existence of residual JE tissue or JE-derived cells after gingivectomization is difficult to rule out [311–313]. As a result, regenerated JE may appear to be derived from oral epithelium but really be derived from residual JE cells. Here, we spotlight a recent series of studies that clarified the existence of a JE stem cell population and developed a new technique for gingivectomies.

Using a lineage-tracing strain of Wnt (a commonly expressed epithelial tissue self-renewal signaling pathway [314]) reporter mice, J. A. Helms and colleagues [75] showed the JE was populated by two distinct populations of cells: slow and fast cell-cycling. Pharmacological induction of apoptosis in G1/S resulted in marked disintegration of the JE compared to surrounding soft tissue, suggesting a higher reliance of JE architecture on replicating cells that surrounding tissues. Indeed, the Wnt reporter and immunostaining for β-catenin (activated by Wnt signaling) demonstrated Wnt-responsive cells at the base of the JE. Then, using a different reporter mouse, the authors found descendants of the basal Wnt-responsive cells fully populated the JE 5 days after tamoxifen delivery, persisted 480 days, and were distinct from cells derived from surrounding oral epithelium. Further investigation showed

a slow-cycling population of Wnt-responsive cells in the base of the JE as a repository of stem cells, which was indeed hinted at by earlier work [307]. This supports a model whereby quiescent and active stem cells coexist in the JE [315].

A follow up study [316] was performed to determine whether this Wnt-responsive population contributed to newly formed or regenerated JE. Using a Wnt reporter system again, a standard gingivectomy was carried out and JE regeneration monitored. Wnt-responsive cells established nearly immediately at the base of the JE and descendants of these Wnt-responsive cells contributed to the JE re-attachment to teeth (Fig. 4a). The newly regenerated JE was eventually entirely composed of Wnt-responsive cells that deposited laminin332. However, as noted, a standard gingivectomy surgery likely does not completely remove the JE. To overcome this historical problem, the authors used a modified procedure to ensure complete excision of the JE. While the surrounding oral epithelium did re-epithelize the tooth, the tissue was keratinized, and no JE-specific structures were noted even at relatively late time-points. Such lack of JE regeneration is different from historical literature and collectively supports the idea that the JE houses a stem cells population that is necessary for its regeneration and homeostasis. These findings suggest disease-states and therapies that potentially destroy the JE, such as percutaneous dental implant placement, may completely inhibit such regeneration. Strategies to reform a Wnt-responsive population within tissue adjacent to teeth or implants or grafting of other JE

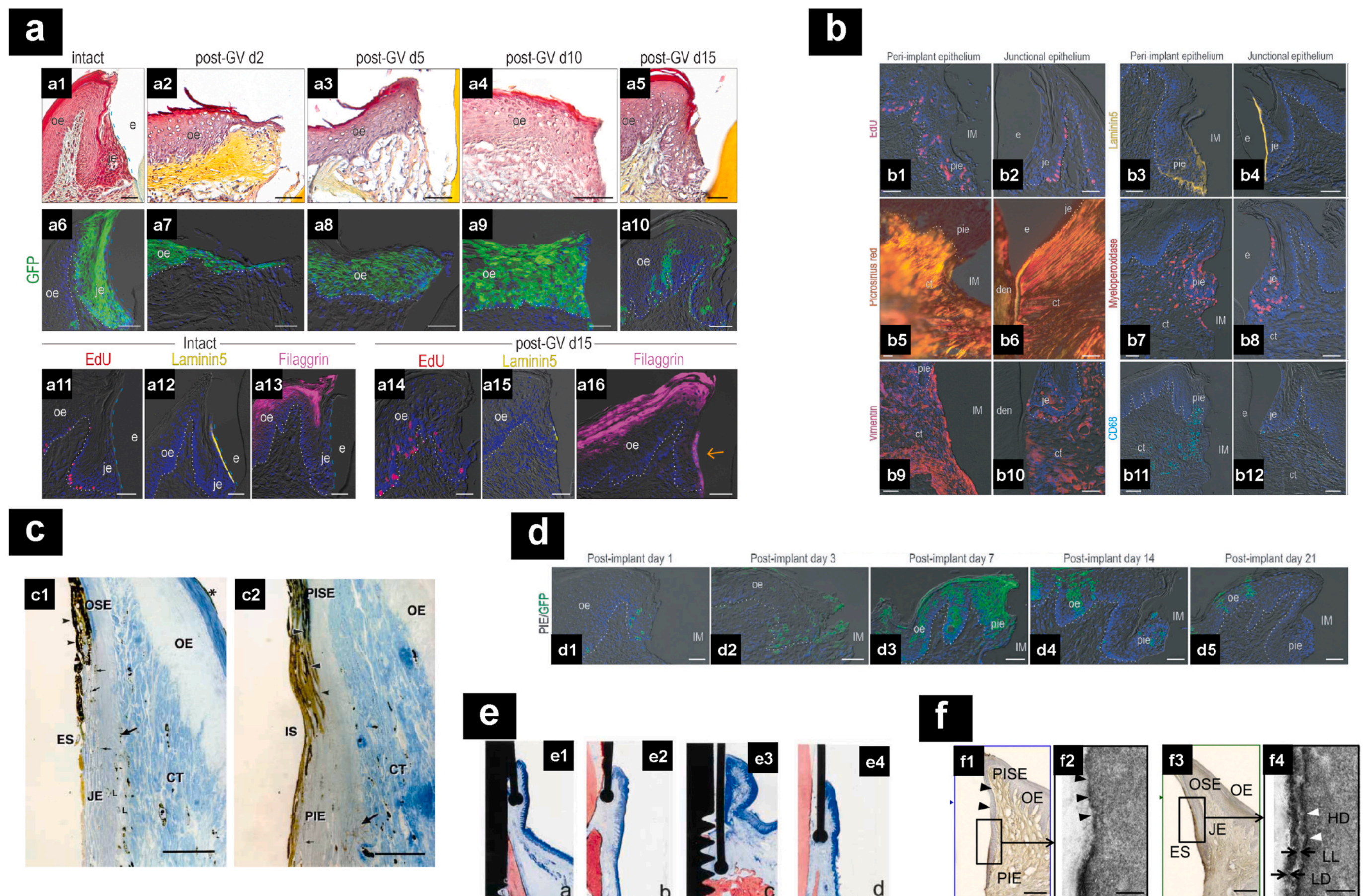

Fig. 4. Junctional epithelium formation and regeneration following gingivectomy and dental implant placement. a. Intact mouse junctional epithelium (**a1**). A circumferential gingivectomy (for complete removal of the junctional epithelium) was performed and samples were pentachrome stained at 2 days (**a2**), 5 days (**a2**), 10 days (**a2**), and 15 days (**a5**) after surgery; a junctional epithelium is not reformed. Similarly, in **a6 – a10**, the green fluorescent protein reporter for Wnt-responsive cells does not distribute to the regenerated, but parafunctional, junctional epithelium compared to control junctional epithelium. In intact samples, EdU (5-Ethynyl-2′-deoxyuridine) (**a11**), laminin-5/laminin332 (**a12**), and filaggrin (**a13**) staining is shown. In contrast, at 15 days after circumferential gingivectomy, EdU (**a14**), laminin-5/laminin332 (**a15**), and filaggrin (**a16**) displayed markedly different staining. Scale bar is 50 μm. Image used with the permission of Wiley [316]. **b.** Comparison between mouse junctional epithelium formed around implants compared to intact teeth in terms of EdU (**b1** and **b2**), laminin-5/laminin332 (**b3** and **b4**), picrosirius red (**b5** and **b6**), myeloperoxidase (neutrophil marker; **b7** and **b8**), vimentin (**b9** and **b10**), and CD68 (monocyte and macrophage marker; **b11** and **b12**). Scale bar is 50 μm. Image used with the permission of Wiley [352]. **c.** Rat junctional epithelium where horseradish peroxidase (HRP) is applied to test the ability of the junctional epithelium to form a barrier with the underling substrate. Here, greater reactivity (dark staining) is seen in the junctional epithelium associated with an implant (**c2**) compared to natural tooth (**c1**), suggesting parafunctional junctional epithelium formation around implants. Scale bar is 25 μm. Image used with the permission of Wiley [358]. **d.** Wnt-lineage tracing, as previously described, following implant placement in mice after 1 day (**d1**), 3 days (**d2**), 7 days (**d3**), 14 days (**d4**), and 21 days (**d5**). Little to no reporter cells are noted in the junctional epithelium. Scale bar is 50 μm. Image used with the permission of Wiley [352]. **e.** Depth on probing of implants and teeth in cynomolgus monkeys (*Macaca fascicularis*); healthy implant (**e1**), healthy tooth (**e2**), peri-implantitis implant (**e3**), and periodontitis tooth (**e4**). Sections stained with Stevenel's blue that was combined with alizarin red S. No scale bar provided. Image used with the permission of Wiley [359]. **f.** Comparison of laminin332 expression in rat junctional epithelium showing reduced expression in implant junctional epithelium (**f1**) compared to natural teeth (**f3**). Simultaneously, reduced – or complete lack – of hemidesmosomes expression is seen in peri-implant junctional epithelium (**f2**) compared to natural junctional epithelium (**f4**), as seen in electron microscopy. Scale bar is 20 μm. Image used with the permission of Elsevier [37]. E, enamel; JE, junctional epithelium; OE, oral epithelium; PIE, peri-implant epithelium; IM, implant; E, enamel; Dent, dentin; CT, connective tissue; ES, enamel space; CT, connective tissues; OSE, oral sulcular epithelium; PISE, peri-implant sulcular epithelium; HD, hemidesmosome; LL, lamina lucida; LD, lamina densa. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

tissue may be necessary.

Others have shown that transcription factor p63, critical for epithelium development and a quintessential marker of epithelial stem cells [317], is present in the basal and superficial layers of the JE [318,319]. Smad2 (mothers against decapentaplegic homolog 2), a mediator of transforming growth factor-β (TGF-β) signaling [320], JE overexpression results in increased apoptosis and decreased proliferation leading the JE being attached to teeth compared to controls [321]. A similar phenotype is seen in p21 and p27 (both are cyclin-dependent kinase inhibitors) double knockout mice [322].

A long series of studies have examined the epithelial rests of Malassez (ERM), which are part of the periodontal ligament around teeth and thought to be important in periodontal tissue regeneration [323,324]. Despite the name "resting," ERMs are derived from the epithelial root sheath integral to tooth formation and, as a result, are a "leftover" component from development that harbor a clonogenic epithelial stem-cell population [325]. These cells produce classical bone/cementum-related proteins [326]. However, the evidence for these cells to regulate JE protein production (like ODAM and AMTN) and regeneration is mixed [326–328]. Further study of ERM in relationship to JE re/generation is necessary to potentially harness the regenerative capabilities of the ERM or its stem cell population.

A final interesting line of experiments has been studying JE formation in tooth reimplantation (also known as replantation) [329]. Optimizing JE regeneration around reimplanted teeth is a pressing concern given approximately one-third of replanted, avulsed teeth are lost, and only one-fourth of teeth show functional healing, by around three years of function [330]. Pioneering studies in the 1970s on rhesus monkeys established that JE regenerated around reimplanted teeth at the histological level within a week but migrated apically by two years [331,332]. This JE regeneration was later determined to be dependent on the presence of residual soft issue on the reimplanted tooth [333]. In a head-to-head study examining JE regeneration around reimplanted teeth and dental implants in rats, the reimplanted teeth generated a JE-like tissue more reminiscent of natural teeth than implants [334]. Pre-treatment of the re-implanted tooth surface with citric acid has been shown to stimulate soft tissue attachment and inhibit epithelial downgrowth [335–337]. These studies pose the question of what surface cues are generated by citric acid and how such treatment could be recapitulated on synthetic percutaneous devices.

5. Peri-implant junctional epithelium

The JE surrounding dental implants is markedly different – parafunctional – from natural JE around teeth. Thus, a variety of biomaterials-based strategies have been undertaken to recapitulate JE physiology around percutaneous devices, with a focus on surface modification and HD formation. We summarize here differences between peri-implant and natural JE and the range of existing strategies to provoke more robust JE formation around dental implants, as well as JE-like regeneration around other percutaneous devices.

5.1. Foundational early studies on peri-implant junctional epithelium

The earliest comparison of JE - a term that had not been coined yet - formation or regeneration surrounding a percutaneous device like a dental implant was the 1952 pioneering work by Loechler and Mueller [338]. These authors compared JE surrounding a cobalt-chromium-molybdenum alloy implant to a healthy tooth and found no morphological differences. A similar report detailed a titanium alloy implant with 12 years of service with a layer of flattened, elongated epithelial cells reminiscent of the JE architecture [339]. Around the same time, James [340] found epithelial attachment onto implants in dogs [340]. However, no evidence for HD formation – or lack thereof – on percutaneous implants was initially investigated given both a lack of understanding of HD formation and suitable analysis methods (in particular, tissue preparation for electron microscopy).

In parallel, a series of studies examined JE morphology and HD formation on natural dentition. A pioneering set of experiments from Listgarten demonstrated the existence of HD mediating attachment of soft tissues to dentition and JE regeneration around teeth following gingivectomies [341–343]. Following these studies, the term "junctional epithelium" was introduced by Anderson and Stern [344] to differentiate the clear differences from the previously used term "epithelial attachment" because the JE was not a "typical" epithelial tissue. Shortly thereafter, due to a collaboration between clinicians and experts in electron microscopy, the first evidence for HD formation on implants in dogs and monkeys was published [30,345]. Later evidence would definitively demonstrate differences in JE surrounding teeth compared to implants.

5.2. Modern investigations of peri-implant junctional epithelium and hemidesmosomes

Recent investigations have shown many differences between peri-implant JE and natural JE [12,346–348]. Once placed, soft tissue around the dental implant migrates over the surface (parallel) and forms a less stable (Fig. 4e), longer (related to epithelial downgrowth discussed in Section 5.3), sparsely populated with HDs, JE [346,349,350]. HDs, when present in the peri-implant JE, tend only be apical compared to natural JE with HDs that span apically to coronally (Fig. 4f) [37]. In addition, the peri-implant JE is more highly fibroblastic, vascularized, and collagenous than natural JE [12,351]. Wnt-responsive stem cells are missing in the peri-implant JE as well (Fig. 4d) [352]. Moreover, the peri-implant JE is more easily damaged by periodontal probing staining, tracers can more easily penetrate, and is slower to regenerate than JE around natural teeth (Fig. 4c) [347,353–355]. Laminin332 distribution during JE regeneration is also different between peri-implant and natural JE (Fig. 4b) [356]. In short, peri-implant JE is easily breached and disturbed, which may lead to bacterial penetration of the internal environment and peri-implant diseases [357]. Characteristics of the peri-implant JE are demonstrated in Fig. 4.

5.3. Epithelial downgrowth around percutaneous devices

Epithelial downgrowth, or marsupialization, around percutaneous implants destabilizes the implant/epithelium interface and provides a moist, warm, and difficult-to-clean pocket for bacteria proliferation [360]. Downgrowth is a natural biological reaction in wound healing and occurs because of the free edge effect, where lack of neighboring cell signals and mechanical cues activate cell migration [361]. Epithelial cells can migrate through damaged collagenous tissue laid down following wounding. However, this migration is halted upon contact with healthy collagenous tissue [362]. Wounding initiates extensive transcriptional changes and cell movement that is achieved in a matter of hours [363]. A key factor for migration initiation is significant upregulation of EGFR [364]. EGFR upregulation may, although it has not been shown, affect HD dynamics, as discussed in Section 2.2.8.

Promoting epithelial cell attachment to implants for stabilization of the implant/epithelium interface is critical to prevent epithelial downgrowth. Five general factors have been identified as contributing to tissue downgrowth **1**) bacterial load at the epithelial/implant interface, **2**) shear mechanical forces experienced by cells at the interface, **3**) topographical, wettability, and physical-chemical characteristic of implant surfaces, **4**) inability of epithelial cells to attach to implant surfaces, and **5)** immunological responses [365]. In response, several biomaterial based strategies have been employed to combat downgrowth (Fig. 5).

For example, porous materials have shown promise in reducing downgrowth in large animal studies (Fig. 5a) [366–370] as has surface topography [371]. Surface coatings of an extracellular domain of E-cadherin [372], keratin isolated from human hair [373], and

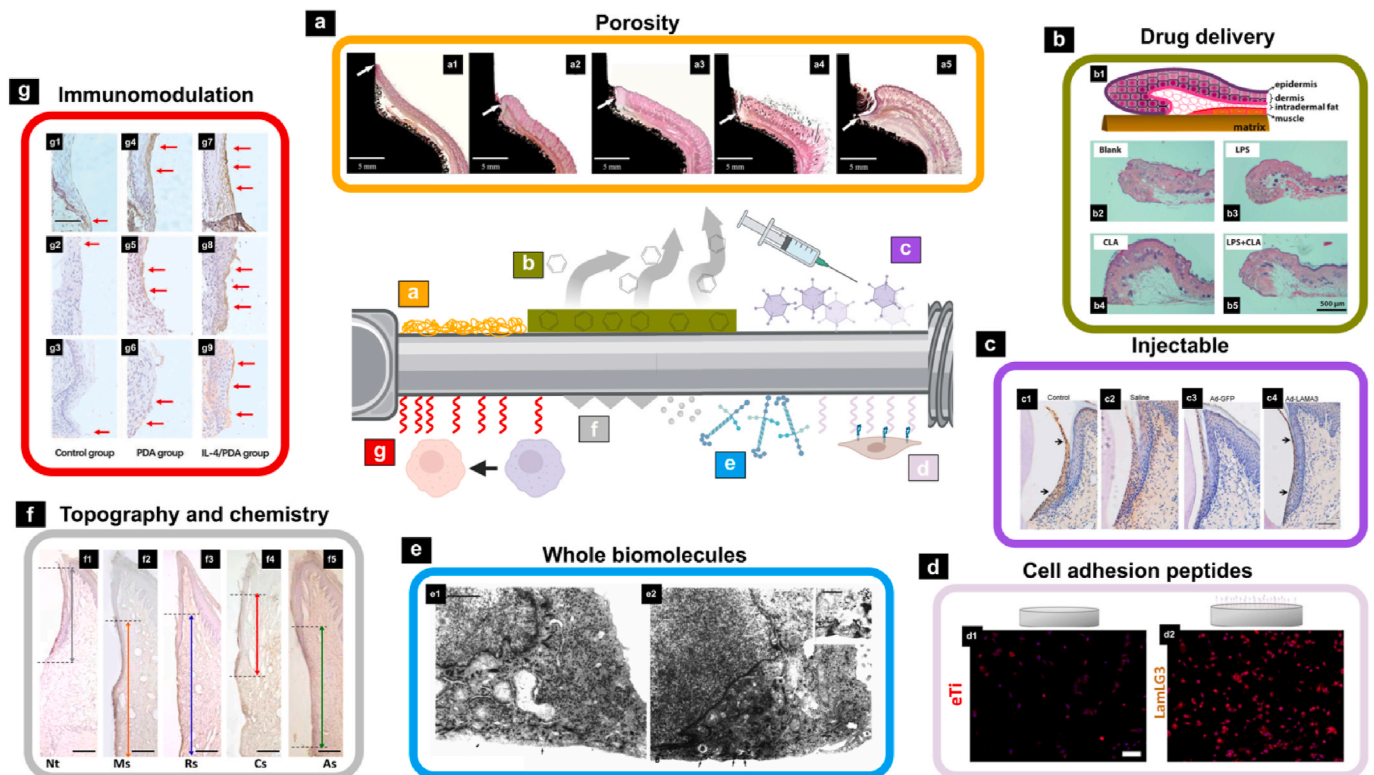

Fig. 5. Biomaterial strategies to promote a junctional epithelium-like attachment to percutaneous devices, and particularly upregulate hemidesmosomes. A range of existing biomaterial strategies, predominately surface modifications for hemidesmosome upregulation, have demonstrated some promise for reducing percutaneous device failure (summarized in center composite). Image created with BioRender (biorender.com). **a.** Implants with a porous percutaneous region were implanted in a load-bearing limb ovine model and gross epithelial downgrowth noted using hematoxylin and eosin staining immediately after implantation (**a1**), 3 months (**a2**), 6 months (**a3**), 9 months (**a4**), and 12 months (**a5**); little downgrowth is noted. Scale bar is 5 mm. Image used with the permission of Wiley [367]. **b.** Conjugated linoleic acid elastomers, capable of biasing macrophage populations toward a pro-regenerative phenotype upon release, were implanted in a dorsal skin mouse model (**b1**). Non-linoleic controls showed skin contraction, which, in this model, is similar to downgrowth (**b2**); this was exaggerated in skin antagonized by lipopolysaccharide (LPS; **b3**). However, groups releasing conjugated linoleic acid reduced contraction/downgrowth both without (**b4**) and with LPS (**b5**). Scale bar is 500 μm. Image used with the permission of the American Chemical Society [380]. **c.** Adenovirus transduction of LAMA3 in a damaged junctional epithelium model results in increased laminin α3 expression in adenovirus-LAMA3 groups (**c4**) compared to adenovirus green fluorescent protein control (**c3**) and saline control (**c2**). A natural, non-damaged junctional epithelium is shown (**c1**) for comparison. Scale bar is 100 μm. Image used with the permission of the American Society of Gene and Cell Therapy [381]. **d.** Keratinocyte expression of collagen XVII on etched titanium surfaces (**d1**) is less than that of peptide-immobilized titanium surfaces (LamLG3) bearing a cell adhesion peptide motif from laminin332 (**d2**). Scale bar is 100 μm. Image used with the permission of the American Chemical Society [382]. **e.** Titanium alloy, which supported the expression of few hemidesmosomes by gingival epithelial cells (**e2**), was coated with a cell-derived matrix rich in laminin332 to increase hemidesmosome formation (**e2**). Electron dense regions on the basal side of the cell are hemidesmosomes. Scale bar is 1000 nm whereas the inset in **e2** is approximately 170 nm. Image used with the permission of Wiley [383]. **f.** Titanium implants were prepared using machining (Ms; **f2**), sandblasting and acid etching (Rs; **f3**), calcium chloride treatment (Cs; **f4**), anodizing (As; **f5**), and compared to a natural tooth (Nt; **f1**). Penetration of a tracer was visualized using horseradish peroxidase. Penetration was similar to Nt in only the Cs, unlike As, Ms, and Rs. Scale bar is 200 μm. Image used with the permission of the American Chemical Society [384]. **g.** Titanium implants coated with interleukin-4 (IL-4) using polydopamine chemistry (PDA) to bias macrophage populations toward a pro-regenerative phenotype. This results in increased laminin332 expression in junctional epithelium in IL-4/PDA groups (three regions shown; **g7** – **g9**) compared to PDA control group (**g4** – **g6**) and non-treated control groups (**g1** – **g3**). Scale bar is 50 μm. Image used with the permission of Wiley [385]. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

hydroxyapatite [374,375] have also been tested *in vitro* to reduce downgrowth. Another potential method is biofunctionalization of surfaces with elastic microfibril interface–located protein 1 (EMILIN1), an extracellular glycoprotein known to reduce keratinocyte migration and proliferation [376,377] Negative pressure wound therapy (NPWT) is sometimes used to help complex wound close through drawing wounds together and removing wound bed exudates [378]. NPWT has been shown to reduce downgrowth in animal models, with the reduction of local proteinases suggested as the mechanism [365,379]. An original approach to reduce downgrowth is based on controlled release of conjugated linoleic acid (CLA), a small molecule known to skew macrophage polarization, from an elastomer in a skin contraction mouse model (Fig. 5b) [380].

5.4. Promoting hemidesmosome formation through biomaterial properties

A promising strategy, inspired by the structural and biological characteristics of the JE, is the upregulation of HDs to improve the clinical outcomes of percutaneous devices. This approach aims to mimic the longevity of percutaneous teeth to reduce epithelial cell migration around percutaneous devices using various strategies. Indeed, promoting HD formation through control of surface physiochemical properties and topography is not a new idea [386]. Early work from the late 1970s to early 1990s proved HD formation was dependent on implant bulk material, smooth surfaces promoted HD formation compared to rough surfaces, and adsorbed protein content controlled HD formation (a detailed history of these early studies may be found elsewhere.) [387–395] Parallel observations were being made from groups investigating implant osseointegration; osseointegration was dependent on implant material, rougher surfaces promoted osseointegration, and

adsorbed protein content controlled osseointegration [396–402]. Since then, only a handful of studies have confirmed that physicochemistry and topography control HD *in vitro* [403] and in rat models [384, 404–406], and specifically that HD formation (in rats at least) is generally higher on zirconia than titanium [407–409]. Overviews of the effects of surface topography on implant soft tissue responses may be found elsewhere [347,410–412]. A recent meta-analysis indicated there was no definitive conclusion from animal studies on the ideal physicochemical properties for peri-implant soft tissue attachment [413]. This inability to properly inform material design exists despite a 1972 review noting that the soft tissue-implant interface was the "Achilles heel" of dental implants [414]. In sharp contrast, investigations into material and surface properties to promote osseointegration have resulted in innumerable publications, patents, and products that have revolutionized dental implant outcomes. A similar revolution for HD formation, or more generally soft tissue healing surrounding percutaneous devices, has yet to occur. However, a few approaches have some proven potential.

One approach – one that has gained recent attention [415] – is the use of biomolecules to promote HD formation. For example, a recombinant adenovirus vector for LAMA3 has proven effective in upregulating peri-implant HD expression in rats when delivered on surfaces or as an injectable (Fig. 5c) [381,416–418]. Functionalization of surfaces with a cell adhesion peptide motif from a globular domain of laminin332 activates HD formation *in vitro* [382,419–422] and in murine [423] and minipig animal models (Fig. 5d) [424]. and Surface adsorption of entire biomolecules, like laminin332 [383,425], is another approach (Fig. 5e).

Alternative, inorganic approaches include hydrothermally treating titanium with calcium chloride to promote release calcium to upregulate HD formation in a rat model [426–428]. UV-treated titanium has also been shown to upregulate HDs compared to non-treated titanium [429]. Finally, sol-gel derived TiO_2 coatings on zirconia upregulate laminin $\gamma 2$ in a full thickness gingival explant model [430], increase interface stiffness between implant and explant tissue [431], and increase epithelial attachment *in vitro* (Fig. 5f) [432]. Immunomodulation strategies for soft tissue healing around percutaneous devices are beginning to emerge (Fig. 5g) [385,433]. An overview of strategies to promote HD formation around percutaneous devices and recapitulate the JE is demonstrated in Fig. 5.

6. Future perspectives and avenues for innovation and inspiration to bioengineer junctional epithelium and hemidesmosomes

The majority of biomaterials-based strategies to recapitulate JE physiology around percutaneous devices have focused on surface modification and HD formation. While this is a highly fruitful starting point, other points of view, in particular from matrix biology and bioengineering concepts, may advance our perspective toward mimicking one or multiple aspects simultaneously of the junctional epithelium. We introduce such concepts drawn from bioengineering and matrix biology that may inspire the next wave of percutaneous device innovations here. Finally, systemic health and other tissues affected by percutaneous devices, such as bone for osseointegrated devices, dictate implant fates. The ultimate solutions for percutaneous device outcomes will likely combine multiple, synergetic approaches.

6.1. Using mechanosensing in hemidesmosome formation and junctional epithelium around percutaneous devices

Keratinocyte mechanosensing regulates fundamental cell functions including proliferation [434], differentiation [435], and migration [436]. While the actin cytoskeleton is a prototypical mediator of mechanoresponses, the keratin network has been strongly implicated in keratinocyte mechanotransduction and is physically linked to HDs [81, 437]. Keratins, as prototypical intermediate filaments, assemble tetramers to produce protofilaments, which then assemble into intermediate filaments made of eight protofilaments [438]. Keratins are post-translationally modified with disulfide bonding to form the cytoskeletal network; as a result, keratins are the most expressed structural protein in keratinocytes [439,440]. Mechanical cues can be transmitted to the nucleus via the perinuclear keratin cage and activate a whole host of responses like the transcriptional regulator Yes-associated protein (YAP) [441]. YAP, of considerable interest in mechanotransduction biology the past decade [442], has in fact been suggested – although not shown – to play a role in the JE [443].

Percutaneous device place may alter local mechanical properties by generating a wound healing provisional matrix, creation of a literal defect in the epithelial tissue where the device emerges from, and juxtaposition of a highly compliant and elastic material (*e.g.,* epithelial tissue) next to a rigid device (such as metallic implant). This may have downstream consequences on HD dynamics. First, altered mechanical properties may change keratinocyte integrin profiles, thus affecting wound healing, HD formation, and integration of mechanical cues [444, 445]. Altered keratin networks, perhaps arising from perturbed mechanical properties, can affect integrin subunit β4 turnover via a plectin-kinase dependent mechanism [446]. Indeed, keratins are necessary for maintenance of intact hemidesmomes [447]. This may also affect keratinocyte matrix deposition and organization [448]. Likewise, tissue stiffening and EGF signaling are intrinsically tied, which may then affect HD dis/assembly [434]. Local mechanical properties can also affect keratinocyte differentiation [449] and laminin332 production [448]. Further investigations are necessary to clarify the relationship between mechanical properties, for example stiffness, and HD formation. This may enable design of percutaneous devices that control local tissue mechanics, including using gradients, to influence wound healing and HD responses.

6.2. Harnessing the junctional epithelium for transferring loads at soft-to-hard tissue interfaces

Soft-to-hard tissue interfaces, such the tendon/ligament-to-bone interface found at rotator cuff and anterior cruciate ligaments or cartilage-to-bone interfaces found in knee joints, are intricately designed sites of load transfer between markedly different tissues [450,451]. A variety of bioengineering strategies have been developed to regenerate these interfaces marked by gradients and optimized spatial distribution of nonmineralized and mineralized regions [452,453]. For example, the natural tooth is partially comprised of the periodontal ligament (PDL), an anisotropic viscoelastic, soft connective tissue between the inner wall of the alveolar socket and roots that transfers loads [454,455]. PDL regeneration around dental implants has long been a goal of oral implantology, in particular the control of collagen fiber orientation around implants [456]. Collagen bundles near the cervical root are orientated horizontally (perpendicular to the tooth) or orientated vertically (parallel) at the apex by mechanosensitive, collagen-secreting periodontal ligament fibroblasts (PDLFs) [457]. This collagen network is disorganized or completely vertical (parallel) in implants [458]. This contributes to the higher stresses and strains bone surrounding implants compared to the bone surrounding teeth, which may lead to bone resorption and implant loosening or even microfracture [459,460]. This may also contribute to possible downgrowth and other soft-tissue structural changes [461].

The role JE plays in transferring loads between the tooth and surrounding soft tissue, perhaps akin to the PDL, is unknown. The noted differences in matrix composition between JE and surrounding tissue, as well as unique geometry of the JE, may implicate it as an important element in load (re)distribution. Mechanotransduction in the oral cavity is poorly studied, although critical to oral morphogenetic processes [462,463]. Evidence does suggest the JE is mechanosensitive; increased application during toothbrushing increases the turnover rate and desquamation of the JE [464]. This may be partially explained by

transient receptor potential cation channel subfamily vanilloid member 4 (TRPV4), a membrane ion channel that transduces external cues into metabolic responses via control of calcium ions [465]. TRPV4 has been shown to regulate metabolic response of chondrocytes to dynamic loading [466] and of mesenchymal stem/stromal cell (MSC) mechanotransduction of oscillatory fluid shear [467]. TRPV4 also contributes to cell-cell junctions in keratinocytes through interactions with β-catenin and E-cadherin [468]. TRPV4-deficinent mice demonstrate wider JE intercellular spacing and greater tracer penetration (*e.g.,* more loosely interconnected tissue), resulting in bone loss, compared to wildtype [73]. The loss of such mechanotransduction elements may contribute to JE vulnerabilities to mechanical stresses.

The RhoA-JNK (c-Jun N-terminal kinase) pathway is also central to mechanotransduction that has been studied in the context of the JE. RhoA-JNK regulates the actin cytoskeleton and responses to mechanical forces through the GTPase activity of RhoA regulating myosin II activity [469] and JNK's role as a MAPK, whose generally strong activation/-phosphorylation and dephosphorylation activity during mechanical stimulation is context dependent [470]. RhoA activation disrupts E-cadherin function in orally-derived epithelial cells by activating JNK in a substrate stiffness-dependent manner; higher stiffness resulted in higher JNK activation [471]. This, concomitant with the lower E-cadherin expression and higher JNK activation in the JE (directly abutting enamel, the stiffest material in the human body) compared to surrounding tissue suggests that, perhaps, the JE does mechanotransduce signals from the tooth. In further support of this model, ODAM has been shown to regulate Rho-A signaling via ARHGEF5 [280]. A better understanding of JE mechanical properties and how JE transmits loads to the surrounding soft tissue, and potential effects on HD formation for example, may enable more biomimetic percutaneous device design for longevity. Indeed, the idea of reducing stress at the device/epithelium is not new but rather vastly unexplored [472]. However, any biomaterial design to take advantage of load transferring must consider that some percutaneous device are anchored, such as to bone, while others are not. HD formation may thus differ.

6.3. Exploiting differences between gingival and skin mucosal healing

Wounds in the oral cavity heal faster than other epithelial wounds [473]. Early work demonstrated lower neutrophil, macrophage, and T-cell infiltration in gingival wounds compared to skin wounds; this is reminiscent of fetal wound healing where neutrophils, macrophages, and lymphocytes are virtually absent [474]. This privileged oral mucosal repair is dependent on TGF-β, prolonged accumulation of tenascin-C (a glycoprotein) [475], strong activation of myofibroblasts [476], differential regulation of apoptosis [477], and presence of saliva in the oral cavity [478].

Intrinsic differences between epithelial cell populations may also explain differential epithelial healing. Epithelial cell microRNAomes [479], the markedly higher ability of oral epithelial cells to reorganize matrix compared to other epithelial sources [480], and differences in expression of keratinocyte migration and proliferation genes, like *PITX2* (a transcriptional regulator) [481], have been shown to underlie wound healing differences. Other work showed oral epithelial cells express three times more HDs than epidermal sources [482]. Bioengineering strategies, like miRNA therapies or controlled release of growth factors inspired by the privileged healing of the oral mucosa, may be useful to stimulate healing of percutaneous devices. Indeed, ideas borrowed from epithelial wound healing literature, an area of literature with decades of success in using tissue engineering and biomaterials for therapies (cell sheets for example) [483], may be advantageous for percutaneous applications.

Differences between gingival and skin healing should be referenced in any percutaneous device design to match the local soft tissue environment. Cues and signals to form HDs likely change as patients age, differ between local skin structure and function (such as orthopaedic limb prostheses compared to indwelling catheters, for example), and baseline HD levels differ between bulk device materials (titanium vs. silicone, for example). The expected lifespan for each percutaneous device, and the fact that some percutaneous devices like indwelling catheters are more readily replaced than dental implants, demands consideration and further research. Indeed, any device modification must also support other functions, such for osseointegration for dental implants.

6.4. Modulating immunology at the soft tissue/percutaneous device interface

Immunological responses to percutaneous devices at the device/epithelium are highly unresolved. For example, infection of percutaneous dental implant results in increased inflammatory infiltrates containing significant levels of macrophages but conclusions beyond that are difficult to draw [484]. Macrophages have been well-described in the biomaterials literature as key regulators of tissue repair [485]. However, other immune cells, such as neutrophils, are influenced by biomaterial properties [486,487]. Despite the intense usage of M1 and M2 designation (pro-vs. anti-inflammatory, respective), many have noted that such as dichotomy is overly simplistic and leads to confusion [488]. The overall potential to modulate immune signaling to create local pro-regenerative environments is immense [489] and has led to reexamination of formerly accepted dogma [490–493]. Indeed, recent attention has been paid to harnessing the body's natural responses to percutaneous devices via immunomodulation instead of simply delivering ineffective antimicrobials [494,495].

Fundamental characterization of such healing responses, including under homeostatic, non-diseased conditions, are needed before improved percutaneous devices and therapies may be developed. Abundant skin wound repair literature as mentioned may guide such studies but the presence of a percutaneous device, or any biomaterial, fundamentally alters wound healing [496]. The oral mucosa may offer design inspiration given its ability to thrive in the presence of a diverse microbiome, mechanical forces from mastication, and dietary challenges [497]. Other diseases associated with loss of HDs in animals, such as equine laminintis [498], or the study of HDs in gut integrity [499], may also be useful to study. Equine laminitis is the loss of attachment and disassembly of HDs due to degradation of laminin332 between the wall of the hoof and the phalanx of the foot at the lamellar dermal-epidermal junction [500,501]. *Streptococci* bacteria upregulate host MMP-9, and to a lesser extent MMP-2, activity that break down local host tissue and seem to be responsible for reduced HD formation [502,503]. Finally, understanding why the JE mounts markedly different cytokine response to bacterial challenges than oral epithelia [67] may unlock advances in understanding JE biology beyond HDs for application to percutaneous devices. Indeed, the effects of bacteria, or bacterial elaborations, on HDs in-and-of themselves remains unstudied to the authors' knowledge.

6.5. Controlling nascent matrix deposition using biomaterials and bioinstructive materials

An emerging biomaterial design paradigm is control of the cell-secreted pericellular matrix. Many materials-based strategies, such as biofunctionalization with cell adhesive cues or controlled mechanical properties, can be overridden and masked by nascent matrix. Moreover, complete control of spatiotemporal presentation of such cues to mimic highly regenerative biological processes, such as development, is difficult [504]. However, control of dynamic reciprocity between cell and matrix may sidestep these drawbacks and lead to more biomimetic, instructive local niches for better biological responses to percutaneous devices [505,506] Degradability, stress relaxation, stiffness, morphology, etc. are potential routes of achieving control of pericellular matrix features, such as structure and/or contents [507–509]. Moreover,

material surface properties in particular have begun to be harnessed to control nascent matrix structure [510,511] and differential activation of rigidity sensing pathways [512]. Indeed, recent work [513,514] has shown that early matrix deposition and remodeling controls cell behavior rather than cues from the biomaterial itself per se. Mechanisms that contribute to keratinocyte polarity and its context to matrix, despite its decades of study in the skin [515], are unknown in the JE but may be a powerful tool to control matrix deposition.

Another emerging biomaterials design paradigm is use of bio-instructive polymers, or materials with no obvious *ab initio* biological properties that reveal a desirable biological activity [516]. These materials, which are typically photocrosslinkable for ease of delivery, have been used to control clonal growth and expansion of pluripotent stem cells [517–519], reduce biofilm formation [520,521], control macrophage polarization [522], support dental pulp stem cell function [523], and for selective cell attachment and culture [524]. An appealing feature of these materials is their lack of biologics and utilization of already Food and Drug Administration (FDA)-approved chemistries, making their potential translation potentially easier. However, an intrinsic challenge is deciphering what chemical moiety(ies) gives rise to particular biological responses, but artificial intelligence and machine learning may aid in advancing this [525]. A final challenge is deciphering the biological mechanism by which these materials influence cells and matrix; few investigators undertake such discover. High throughput screening of topographies, such as the TopoChip [526], is a conceptually similar, promising strategy [527]. These approaches may aid investigators in developing more effective percutaneous devices that last decades.

6.6. Other biomaterial design paradigms for bioengineering junctional epithelium and hemidesmosomes

An interesting avenue for future work to upregulate HDs may be laminin-based biomaterials, which are highly popular in neural tissue engineering [528,529]. While control of laminin structure on surfaces or in hydrogels, as well as sourcing of pure isolates and immunogenicity, are challenges to working with entire laminin biomolecules, smaller laminin-derived peptide sequences may be equally powerful [530]. It has also been reported dentin has a higher adsorption affinity than titanium for basement membrane biomolecules [531]. Such differences may affect elaborated biomolecule retention in the matrix and may contribute to parafunctional JE regeneration on percutaneous dental implants. Material properties could be exploited to control biomacromolecule adsorption and so biological outcomes [532].

A recent area of investigation has been tissue adhesives with high toughness [533] and remarkable speed of complete bond formation [534] on wet substrates [535]. Derivatization of such adhesives for application to percutaneous devices/epithelium tissue interfaces may "jump start" attachment and reduce failure rates. Early examples have been demonstrated [536,537]. Finally, many percutaneous device materials, such as those for dental Class II and Class V restorations, have marked cytotoxicity leading to poor gingival attachment *in vivo.* [538,539] Basic steps to alleviate such obviously detrimental tissue reactions must be taken before more complex biological responses are engineering into materials. Use of appropriate cell culture systems, such as keratinocytes, or co-cultures for JE and/or HD applications, may be a first step.

Better incorporation of tissue engineering methods may be useful to understand the JE and derivative such understanding for more efficacious epithelial attachment and regeneration around percutaneous devices. For example, a 1975 study [345] used what would be called a bioreactor today to investigate HD formation within an oral epithelium tissue model. Bioreactors, and broader utilization of organotypic-reconstructed human oral epithelium gingiva models [540], may aid investigators. A related point is the relatively small number of studies using animal models for percutaneous devices as a whole and particularly JE animal studies [541]. Developing quality, wide-spread animal models may contribute to a firmer basic understanding of JE biology for eventually applications to percutaneous devices. Indeed, only a handful of histological examination of human tissues have been published given ethical concerns of retrieving tissue surrounding from healthy implants [542–546].

A final, patient-centered point should be made. It has been well documented that the overall systemic health of the patient can affect percutaneous device outcomes. For example, radiotherapy reduces osseointegrated dental implant lifespans [547] and osteoporosis reduces osseointegrated orthopaedic percutaneous device lifespans [548]. Likewise, a smaller body of evidence suggests that systemic diseases and treatments affecting soft tissue quality and regeneration harm percutaneous device outcomes. For example, patients with epidermolysis bullosa receiving dental implants report mixed outcomes [549,550]. Precision medicine may aid development of better treatment modalities for these patients.

7. Conclusions

The percutaneous device dilemma, despite being identified decades ago, persists and patients suffer. Natural percutaneous organs, like the tooth's extracellular matrix mediating the "device"/epithelium interface, may serve as exquisite examples to inspire percutaneous device design, particularly through surface engineering. Recapitulation of junctional epithelium characteristics and hemidesmosome formation is a promising – and growing – biomaterial strategy. Next-generation strategies will induce hemidesmosome formation, provoke tissue matrix production, and synergize with the body's immune system. Material complexity must be distilled to the absolute minimum required to delivery biomaterials that stand a chance of regulatory clearance. Collaboration between clinicians in relevant medical specialties – orthopaedic, dental, urology, etc. –, matrix biologists, and bioengineers may prove to be transformative. Materials science and basic biology must underlie all investigations. Innovation should be fueled by our willingness to cross disciplinary boundaries to ultimately deliver the next generation of technologies for long-lasting permanent percutaneous devices.

CRediT authorship contribution statement

Nicholas G. Fischer: Conceptualization, Investigation, Visualization, Writing – original draft. **Conrado Aparicio:** Conceptualization, Investigation, Supervision, Funding acquisition, Writing – review & editing.

Declaration of competing interest

None.

Acknowledgements

This work was supported by the NIH/NIDCR under awards R01DE026117 (CA), F30DE029105 (NGF), and T90DE0227232 (NGF). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. This work was supported by the Assistant Secretary of Defense for Health Affairs through the Peer Reviewed Orthopaedic Research Program (PRORP) under Applied Research Award No W81XWH-20-1-0563 (CA). The U.S. Army Medical Research Acquisition Activity, 839 Chandler Street, Fort Detrick MD 21702-5014 is the awarding and administering acquisition office. Opinions, interpretations, conclusions, and recommendations are those of the authors and are not necessarily endorsed by the Department of Defense. The work was also supported by a 3M Science and Technology Fellowship (NGF). The funding bodies had no role in study design, the collection, analysis and interpretation of

data, in the writing of the report, and in the decision to submit the article for publication. CA acknowledges support from the Fundació Bosch Aymerich through a FBA-BIST-UIC fellowship. IBEC is a member of the CERCA Programme/Generalitat de Catalunya.

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